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THE UNIVERSITY OF CONNECTICUT
HEALTH CENTER

Department of Laboratory Medicine
June 9, 1969

cc: Epstein
Kamburg

Dr. Joshua Lederberg
Department of Genetics
Stanford University Medical Center
Stanford, California 94305

Dear Doctor Lederberg:

Thank you for your gracious note, and for the reprint of your essay which was published in the Congressional Record. I concur wholeheartedly with the views which you expressed regarding the carcinogenic hazards of occupational and environmental exposures to nickel.

Our recent demonstration that $Ni(CO)_4$ is a potent inhibitor of RNA polymerase activity in mammalian systems furnishes a mechanism whereby nickel can produce acute alterations in the expression of genetic information. The possible relevance of this finding to the initiation of nickel carcinogenesis is suggested by similarities between the inhibitory effects of $Ni(CO)_4$ upon RNA synthesis, and the effects of several other chemical carcinogens, including aflatoxin, 4-nitroquinoline-N-oxide, and actinomycin D.

As yet, no one has studied the effects of $Ni(CO)_4$ upon nucleic acid synthesis in bacterial or viral systems. The major deterent to such studies has been the extreme toxicity of $Ni(CO)_4$, and hence the necessity of safeguards and monitoring devices to protect the investigators who employ $Ni(CO)_4$. To avoid this disadvantage, we have arranged to have $Ni(CO)_4$ ampouled in 0.5 vials which can be handled safely in an ordinary fume hood. Perhaps you or your colleagues might consider employing $Ni(CO)_4$ in your studies of mutagenesis.

In your letter, you emphasized the desirability of identifying the chemical form in which Ni is emitted in gasoline exhaust. I believe that this task can now be accomplished by use of our new gas chromatographic method for detection and measurement of $Ni(CO)_4$.

Your attention is directed to the possibility of a co-carcinogenic relationship between nickel and 3,4-benzpyrene. Both of these compounds are known to be present in tobacco smoke, automobile exhaust, and polluted urban atmospheres. We have shown that $Ni(CO)_4$ blocks the induction of benzpyrene hydroxylase, the principal detoxification mechanism for polycyclic aromatic hydrocarbons. Moreover, unpublished studies in our laboratory have shown that exposures of rats to $Ni(CO)_4$ prolong the retention of 3,4-benzpyrene in the lungs and liver. These indications of carcinogenic synergism of nickel and benzpyrene may be especially pertinent, since the Surgeon General's Report

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on Smoking and Health emphasized that the carcinogenicity of cigarette condensates is greater than the sum of the known carcinogenic constituents.

Enclosed are tables (from a paper in preparation) which list the available data on nickel content of cigarettes, urban atmospheres and asbestos fibers. In accordance with your request, I have also enclosed reprints and preprints of our recent studies. Please let me know if there is any way in which I can be helpful to you.

With best wishes, I am

Sincerely yours,

F. William Sunderman, Jr., M.D.
Professor and Head

FWS:nii
Enclosures